Review Article

Approach to bleeding patient

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ABSTRACT

Managing a bleeding patient is very challenging for the perioperative physician. Bleeding in a patient would be due to inherited or acquired disorders of haemostasis. Identifying the patients at risk of bleeding and utilising prophylactic treatment protocols has good outcomes. Along with clinical signs, trends in monitoring coagulation parameters and analysing blood picture are necessary. Management of patients in the postoperative period and in intensive care unit should be focused on normalization of coagulation profile as early as possible with available blood and its products. Available recombinant factors should be given priority as per the approved indications. Exploring the surgical site should be considered for persistent bleeding because haemodynamic compromise, excessive transfusion of fluids, blood and its products and more inotropic support may have a negative impact on the patient outcome.

Key words: Factor VII, haemophilia A, haemorrhage

INTRODUCTION

Managing a bleeding patient is very challenging for the emergency physician, intensivist or preoperative physician. Prompt resuscitation is essential and should be guided by clinical signs and trends in monitoring.[1] Patients, usually, have changes in heart rate, blood pressure, slow capillary refill time, tachypnea, change in temperature, decreased urine output and altered blood gas analysis. Some of the features like haemodynamic changes, urine output and blood gas alteration, may be late signs.[2] Prompt identification of unstable patients and resuscitation is necessary. Haemoglobin and coagulation variables should be checked. Blood and its products should be available and transfused when necessary. Preoperatively a thorough history is paramount in evaluating a patient for a possible systemic bleeding disorder. In addition to asking the patient about spontaneous bleeding episodes in the past, responses to specific haemostatic challenges should be recorded. A bleeding tendency may be suspected if a patient previously experienced excessive haemorrhage after surgery or trauma, including common events such as circumcision, tonsillectomy, labour and delivery, menstruation, dental procedures, vaccinations, and injections; similar events in the family members need to be considered. The symptoms that may be elicited could be in the form of bruising that may be spontaneous or recurrent; large bruises on the trunk are more indicative of a bleeding disorder and history of prolonged bleeding after minor cuts or abrasions, nose bleeds lasting >10 min despite compression (especially in children), severe menorrhagia causing anaemia, bleeding from gums, postpartum haemorrhage respectively. Also, one should enquire regarding current medications including aspirin, nonsteroidal anti-inflammatory drugs, warfarin and complementary/alternative preparations. Drug interactions between warfarin and other medications that prolong the international normalized ratio (INR) should be considered.

A systemic look for signs like pallor, haemodynamic status, lymphadenopathy or hepatosplenomegaly is mandatory. During physical examination, skin, palate and gums are checked for bruising, purpura and ecchymosis, fundi for retinal haemorrhages and joints for haemarthrosis.

DISORDERS OF HAEMOSTASIS

Coagulation problems may be due to disorders of

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haemostasis, disorders of thrombosis or may be due to involvement of both.

Inherited disorders

Haemophilia A and B

These disorders are due to deficiency of factors VIII and IX respectively, and are X-linked recessive, affecting males born to carrier females [Table 1]. Spontaneous bleeding occurs in severe cases when there is <2% of coagulation factors. Patients with mild haemophilia (>10% of coagulation factor) may also bleed excessively after trauma and surgery which is very important in obstetric patients.[3]

For major surgeries in haemophilia patients, target factor VIII concentration of 100% is to be maintained for 5-7 days postoperatively. For minor procedures, target factor concentration of 50% is necessary from the 1st day of surgery. Minor trauma or more severe bleeding requires plasma levels of factor VIII 30-50 IU/dl and dose required to maintain it is 15-25 U/kg [Table 2]. Surgery and major trauma require plasma concentration of 80-120 IU/dl of factor VIII and dose required is 40-60 IU/kg.[4] It is recommended that surgery in haemophilia patients should be performed in specialised centres with expertise in coagulation disorders. The perioperative replacement therapy (target factor level and duration) in haemophilia patients should be as per published guidelines.[5]

Table 1: Inherited bleeding disorders

Disorder	Pathophysiology/ deficiency	Inheritance
Haemophilia A	VIII	X linked recessive
Haemophilia B	IX	X linked recessive
Haemophilia C	XI	Autosomal dominant or recessive
VW disease	VW factor	Autosomal dominant or recessive
Factor X deficiency	Factor X	Autosomal recessive
Factor V deficiency	V	Autosomal recessive
Factor VII deficiency	VII	Autosomal recessive
Prothombin deficiency	II	Autosomal recessive
Afibrinogenemia/ dysfibrinogenemia	I	Autosomal dominant

VW factor – Von Willebrand factor

Haemophilia C

Haemophilia C is caused due to deficiency of factor XI. It has different modes of inheritance and is autosomal recessive in Ashkenazi Jews. In this condition, bleeding diathesis will not correlate with factor XI concentration. Factor XI may rarely be required and fresh frozen plasma (FFP) is usually sufficient.

Von Willebrand disease

Here the defect is in Von Willebrand factor (VWF) which is produced by Weibel–Palade bodies of platelets whose function is to adhere platelets to sub endothelial layers. This is diagnosed by estimation of factor VIII C concentration, VWF antigen (VWFAg), and platelet activity with ristocetin cofactor (VWR Cof). The use of blood products can be avoided in these patients; minor bleeding can be managed with tranexamic acid. Desmopressin acetate (DDAVP) of 0.3 mcg/kg 90 min before operation is helpful in preventing bleeding by increasing the levels of VWFAg and factor VIII levels to normal. Factor VIII concentrates and plasma products should help overcome situations with bleeding.[4,5]

It is recommended that patients with Von Willebrand disease (VWD) should be managed perioperatively in collaboration with a haematologist. DDAVP is the first-line treatment for minor bleeding/surgery in patients with VWD. For major bleeding/surgery replacement of VWF along with plasma derived products are required. Antifibrinolytic drugs can be used as haemostatic adjuncts. Platelet transfusion may be used only in case of failure of other treatments.[5]

Inherited platelet disorders

Patients with platelet disorders like Glanzmann's disease and Bernaurd–Soulier disease should be transfused with platelet concentrates to prevent acquisition of specific antibodies to platelets. Preoperative haemostasis in patients with inherited platelet disorders is recommended and desmopressin to be used to prevent/ control perioperative bleeding. Antifibrinolytic drugs

Table 2: Factors and dosage

Material	Factor VIII	VW factor	Advantages	Disadvantages
DDAVP		-	No risk of infection	Only effective in mild cases
Intermediate purity factor VIII concentrate	20-50 IU/ml	20-50 IU/ml	Convenience	Plasma derived nonfactor VIII proteins present
High purity factor VIII concentrate	5000 IU/mg	-	Convenience	Expensive
Recombinant factor VIII	5000 IU/mg	-	Pure, no risk of infection	Very expensive, limited supply

VW factor – Von Willebrand factor; DDAVP – Desmopressin acetate

should be used as haemostatic adjuncts. Treatment with rFVIIa should be considered in patients with Glanzmann thrombasthenia undergoing surgery.[5]

Acquired disorders

Acquired bleeding disorders can occur spontaneously but most have an identifiable root cause. It can be internal bleeding or it can be bleeding into skin and soft tissues. Different causes of acquired bleeding may include trauma, different medical conditions of the patient and certain medications altering the coagulation cascade at different levels.

TRAUMA

In bleeding trauma patients, we should minimize the time between admission and arrival in the operation theatre for improved survival.[6,7] We should not rely on a single laboratory haematocrit as a marker for bleeding.[6,7] Serum lactate and base deficits are very sensitive indicators of hypovolemic shock.[6,7] Routine measurement of prothrombin (PT), activated partial thromboplastin time (APTT), fibrinogen and platelet count are useful in detecting coagulopathy.[6,7] Target mean arterial pressure (MAP) >80 mm of Hg should be maintained in haemorrhagic shock.[6,7]

Crystalloids are the first choice for fluid replacement; hypotonic solutions like Ringer lactate are to be avoided in traumatic brain injury.[6,7] In unstable patients, colloids and hypertonic saline are good choices.[6,7] Vasopressors should be used to maintain MAP in the absence of response to fluid therapy.[6,7] Inotropic agents should be added in the presence of myocardial dysfunction.[6,7] In trauma, up regulation of endothelium thrombomodulin occurs, which form complexes with thrombin, that leads to coagulopathy. Antifibrinolytic agents should be administered to trauma patients at risk of significant haemorrhage.[6,7] Ionized calcium should be maintained in massive transfusion.[6,7] The system of 1:1:1 whole blood: FFP: Platelet rich plasma (PRP) should be followed. If plasma fibrinogen is <1.5-2 g/L fibrinogen concentrate or cryoprecipitate should be administered.

Platelet count should be more than 1,00,000/mm^3 in on-going bleeding.[6,7]

Bleeding in patients on oral anticoagulants and antiplatelet drugs

Desmopressin 0.3 mg/kg should be used in patients treated with platelet inhibiting drugs or VWD. Desmopressin should not be used routinely in bleeding trauma patients.[6,7] Prothrombin complex concentrate (PCC) should be used in patients on Vitamin K dependent oral anticoagulants.[6,7] In patients on rivaroxaban, apixaban PCC of 25-50 U/kg should be used. PCC is of no use in patients on oral, direct thrombin inhibitors like dabigatran.[6,7]

For intra- or post-operative bleeding clearly related to aspirin, clopidogrel and prasugrel platelet transfusion should be considered. Platelet transfusion may be ineffective for treating bleeding clearly related to ticagrelor when given 12 h before. Severe bleeding associated with intravenous (IV) unfractionated heparin (UFH) should be treated with IV protamine sulphate in a dose of 1 mg/100 IU UFH given in the preceding 2-3 h. Severe bleeding associated with subcutaneous UFH unresponsive to IV protamine sulphate in a dose of 1 mg/100 IU UFH could be treated by continuous administration of IV protamine, with a dose guided by APTT. Severe bleeding related to subcutaneous low molecular weight heparin (LMWH) should be treated with IV protamine at a dose of 1 mg per 100 anti-FXa units of LMWH administered.

Severe bleeding associated with subcutaneous LMWH and unresponsive to initial administration of protamine could be treated with a second dose of protamine (0.5 mg per 100 anti-FXa units of LMWH administered). Severe bleeding associated with subcutaneous administration of fondaparinux administration of rFVIIa could be considered.[5]

Microangiopathic haemolytic anemia

It is of immune origin. It is of two forms, thrombotic thrombocytopenic purpura (TTP) and haemolytic syndrome (HUS). TTP presents with predominant neurological deficits due to thrombosis of small cerebral vessels. HUS is associated with renal dysfunction and managed with total plasma exchange and cryoprecipitate supernatant plasma which is deficient in high molecular weight Von Willebrand multimers. IV immunoglobulin (Ig) 0.4 mg/kg should be given for 5 days and target platelet count should be 80,000/mm^3.

Chronic renal failure

Renal failure leads to qualitative defects in platelets which can increase bleeding. It can be corrected by DDAVP. There will be increased concentration of factor VIII related antigen, factor VIII procoagulant activity (VIIIC) and decreased VW activity (VIII F).

The functional abnormality of factor VIII explains prolonged postoperative bleeding.

Conjugated oestrogen therapy should be used in uraemia and desmopressin should be considered for reducing bleeding during surgery and for managing acute bleeding in uraemic patients. There is no evidence to support use of rFVIIa.[5]

Liver disease

Liver is the site of production of major coagulation factors. Bleeding in patients with liver disease can be of multifactorial aetiology. Portal hypertension leads to splenic sequestration of platelets which contributes to thrombocytopenia. There can be reduced levels of coagulation factors V, VII, IX, X, XI and reduced PT in liver failure. In contrast, factor VIII levels are often elevated. Vitamin K dependent clotting factors (II, VII, IX, X) may be defective in function as a result of decreased carboxylation (from Vitamin K deficiency or intrinsically impaired carboxylase activity). Fibrinogen levels in patients with advanced cirrhosis are found to be reduced but can be within the normal range in patients with stable disease. Oral or parenteral Vitamin K should be given if deficiency is suspected especially in patients with cholestasis, malnutrition or antibiotic therapy. Despite PT, APTT and INR indicating coagulopathy in chronic liver disease (CLD), global coagulation tests (thrombin generation and thrombelastography [TEG]/ROTEM) suggest that the haemostasis is balanced in stable CLD. Mild to moderate prolongation of the preoperative PT and INR do not predict bleeding in patients with CLD. For preprocedural correction of mild to moderately elevated INR, the use of FFP is not recommended in patients of CLD.[5]

Systemic lupus erythematosus

Systemic lupus erythematosus may be associated with immune thrombocytopenia. It may also be associated with the production of antibodies to glycoprotein Ib.[4]

Haematological malignancies

Disseminated intravascular coagulation (DIC) occurs in promyelocytic leukemia. Abnormal platelets lead to prolonged bleeding. This can be usually managed by restoring blood count parameters and transfusing PRP. In the case of bleeding malignancies like bronchogenic carcinoma, it is better to embolise the target vessel preoperatively to prevent profuse bleeding. Single donor platelets are preferred over regular PRP to prevent alloantibody mediated refractoriness to platelets as they are potential bone marrow transplant recipients.

Bleeding after massive transfusion

Traditionally replacing total blood volume in 24 h is called as massive transfusion. Other practical definitions include loss of half the total blood volume within 3 h; use of 6 units of packed red blood cell (RBC) in 12 h, etc (see the section of massive blood transfusion in this issue). Specific transfusion of coagulation factors in the form of FFP and PRP should be given until bleeding stops.

Bleeding in cardiac surgery

Significant bleeding is seen in complex cardiac surgeries and prolonged procedures. Patients with a history of coagulation abnormalities, extremes of age, renal insufficiency, prolonged bypass time, emergency surgery, patients with congestive heart failure and shock are the patients who may bleed more.[8,9] Platelets exposed to a large area of inert material leads to retention rendering patient thrombocytopenic. Hypothermia inhibits production of thromboxane A2 which aggregate spontaneously and prematurely. PRP transfusion is helpful in such situation after prolonged exposure to cardiopulmonary bypass (CPB).

Incomplete heparin neutralization and heparin rebound is associated with more postoperative bleeding. Heparin induced thrombocytopenia (HIT) is another entity where bleeding occurs because of the formation of antibodies to PF4 and consequent thrombocytopenia. It can be managed with immediate stoppage of heparin and use of heparin alternatives like bivalirudin and platelet transfusion.

Intraoperative tranexamic acid or epsilon-aminocaproic acid administration should be considered to reduce perioperative bleeding in high, medium and low risk cardiovascular surgery. Tranexamic acid should be applied topically to the chest cavity to reduce postoperative blood loss following coronary artery bypass graft surgery. It is recommended that fibrinogen concentrate infusion guided by point-of-care viscoelastic coagulation monitoring should be used to reduce perioperative blood loss in complex cardiovascular surgery. We suggest that in patients with intractable bleeding during cardiovascular surgery, once conventional haemostatic options have been exhausted, recombinant FVIIa may be considered.[5]

Thrombocytopenia in pregnancy

Causes of thrombocytopaenia in pregnancy include benign gestational thrombocytopenia, HELLP syndrome, or they could have autoimmune or congenital basis or associated with hypersplenism.

Corticosteroids are useful. Extreme cases respond to methyl prednisolone, IV immunoglobulins are also useful. TTP and HUS of pregnancy can be managed with FFP and avoiding PRP.

Disseminated intravascular coagulation

Another important entity for severe bleeding which will be discussed in further section in this volume.

MANAGEMENT OF BLEEDING PATIENT IN INTENSIVE CARE UNIT

As opposed to regular preoperative standard management of coagulopathies, patient management in intensive care unit should be done only in case of upcoming invasive procedures or patients with on-going bleeding.[10] Though the ratio of 1:1 RBC: FFP holds good for massive transfusion in trauma patients, a restrictive approach is preferred in intensive care unit (ICU) patients because of the high incidence of acute respiratory distress syndrome due to transfusion related acute lung injury.[10] In case of DIC when INR >1.5 it is suggested to transfuse FFP, maintain platelet count of >50,000/mm^3 and fibrinogen levels >150 g/dl.[10] Thrombocytopenia occurs in 20% of ICU patients and the causes may be various. HIT, immune thrombocytopenia, DIC due to sepsis are common. Always request the laboratory for fragmented RBC (schistocytes) to distinguish DIC from TTP. Maintain platelet count of >50,000/mm^3 in unstable bleeding patients. Where bleeding into central nervous system is suspected, maintain high platelet counts (1,00,000/mm^3).[10] [Table 3].

MANAGEMENT OF BLEEDING WITH BLOOD PRODUCTS

Cryoprecipitate: It is prepared by thawing a single unit of FFP at 1-6°C. Cryoprecipitate contains VWF, factor XIII, fibrinogen and fibronectin. It is mainly used to manage bleeding in acquired hypofibrinogenemia. One unit per 10 kg will raise fibrinogen by approximately 50 mg/dl, whereas 30 ml/kg FFP is required for raising plasma fibrinogen by 1 g/L. International guidelines 2009 recommend minimum fibrinogen levels of 80-100 mg/dl.[11] But European guidelines recommend higher fibrinogen levels (150-200 mg/dl) for perioperative period.[12] Therapeutic response to cryoprecipitate can be measured by plasma fibrinogen levels or TEG.

Fibrinogen concentrate as part of treatment protocols is now being considered. Fibrinogen substitution in cases of hypofibrinogenemia has the potential to reduce bleeding, requirement for transfusion and thus reduce morbidity and mortality. A systematic search for randomized controlled trials (RCTs) and nonrandomized studies investigating fibrinogen concentrate in bleeding patients included 30 studies out of 3480 identified (7 RCTs and 23 nonrandomized). In these seven RCTs, a total of 268 patients were included (165 adults and 103 paediatric), and all were found to be at a high risk of bias and none reported a significant effect on mortality. Two RCTs found a significant reduction in bleeding and five RCTs found a significant reduction in transfusion requirements. The 23 nonrandomized studies included a total of 2825 patients, but only 11 of 23 studies included a control group. Three out of 11 found a reduction in transfusion requirements while mortality was reduced in two and bleeding in one. In the available RCTs, which had significant shortcomings, it was found that a significant reduction in bleeding and transfusions requirements was seen. However, data on mortality were lacking. The evidence for use of fibrinogen concentrate in bleeding patients, primarily in elective cardiac surgery is weak; use of fibrinogen across all settings is only supported by nonrandomized studies with shortcomings. Whether fibrinogen concentrate has a routine role in the management of bleeding and coagulopathic patients' needs to be studied further.[13]

PLASMA DERIVED AND RECOMBINANT FACTOR CONCENTRATES

In bleeding due to congenital disorders or thrombophilic disorders, plasma recombinant factor is preferred over FFP with cryoprecipitate to replace specific protein. Recombinant factors have the major advantage that it does not carry a risk of transmitting viral diseases.

Factor VII concentrate

Factor VII concentrate usage has increased because of development of antibodies to factor VIII and a major advantage is it has factor VIII bypassing activity. Factor VII has wide spread usage in trauma and post-CPB. Recently, because of its off label usage, Food and Drug Administration has placed a black box warning on its potential risk for thrombotic events.

Table 3: Summary of management of Bleeding patients due to various aetiology

Clinical recognition	Investigation	Surgical control/medical management
Inherited disorders		
Haemophilia A and B	Factor VIII assay and factor IX assay	20-50 IU/ml of factor VIII concentrate
Spontaneous bleeding in severe cases, bleeding after trauma or surgery in mild to moderate cases		
Haemophilia C	Factor XI assay	FFP containing adequate amount of factor IX
VW disease	Factor VIII protein C and VWFAg, VWiCof	DDAVP 90 min before surgery 0.3 mcg/kg-first line in minor procedures Factor VIII concentrate >100 units/ml or replacement of VWF with plasma products
Inherited platelet disorders	Anti-HPA 1a antibodies	Platelet concentrate, desmopressin for prevention/ control of perioperative bleeding
Acquired disorders		
Trauma	PT, APTT, fibrinogen and platelet counts	Vide above in trauma section
Bleeding in patients on oral anticoagulants and antiplatelet drugs	PT, APTT, platelet count and platelet aggregometry	Platelet transfusion and desmopressin 0.3 mg/ kg should be used in patients treated with platelet inhibiting drugs. PCC should be used in patients on Vitamin K dependent oral anticoagulants. Reversal with protamine 1 mg for 100 U of heparin
Microangiopathic hemolytic anemia TTP and HUS. TTP presents with predominant neurological deficits due to thrombosis of small cerebral vessels. HUS has renal dysfunction	Platelet count	Managed with total plasma exchange and cryoprecipitate supernatant plasma which is deficient in HMW VW multimers. IV Ig 0.4 mg/kg should be given for 5 days. Target platelet count should be 80,000
Bleeding in cardiac surgery	Thromoelastography, activated clotting time, PT, APTT, sonoclot, platelet function analyser	Identify surgical cause of bleeding by re exploration. Blood and its component therapy as appropriate. Tranexamic acid topical and/or systemic, EACA for minor to intermediate bleeding. Protamine for heparin induced bleeding. Stop heparin and start alternatives if HIT is diagnosed
Thrombocytopenia of pregnancy	Platelet count	Corticosteroids are useful. Extreme cases respond to methyl prednisolone, IV. Igs are also useful TTP and HUS of pregnancy can be managed with FFP and avoiding PRP
Chronic renal failure	Factor VIII RA, factor VIII procoagulant activity (VIIIC) VW activity (VIII F) Platelet function analyzer	DDAVP, anemia should be corrected erythropoietin and iron supplements
Liver disease	APTT, platelet count, liver function tests	Treat as per the deficiency. In Vitamin K deficiency supplement IV Vitamin K
SLE	Platelet count	PRP
Haematological malignancies	Platelet count and platelet function analysis	SDP or PRP
Massive transfusion	Platelet count, coagulation factor levels	Component therapy

VW – Von Willebrand; VWiCof – Von Willebrand cofactor; TTP – Thrombotic thrombocytopenic purpura; HUS – Haemolytic syndrome; SLE – Systemic lupus erythematosus; VWFAg – Von Willebrand factor antigen; HPA – Human platelet antigen; PT – Prothrombin; APTT – Activated partial thromboplastin time; VIII RA – VIII related antigen; FFP – Fresh frozen plasma; PCC – Prothrombin complex concentrate; HMW – High-molecular-weight; IV – Intravenous; Ig – Immunoglobulin; EACA – Epsilon-aminocaproic acid; HIT – Heparin induced thrombocytopenia; DDAVP – Desmopressin acetate; SDP – Single donor platelets; PRP – Platelet rich plasma

Prothombin complex concentrates

Sterile lyophilized concentration of factor II, VII, IX and X. It is an acceptable alternative in Jehovah's Witness patients, following massive transfusion, post-CPB and liver failure.

SUMMARY

In case of bleeding during the perioperative period, our goal is to normalize the patient's coagulation profile as early as possible. We should prevent bleeding by utilizing prophylactic treatment protocols and checklists. In case of significant bleeding it is better to re-explore the surgical site as haemodynamic compromise, more inotropic support and extreme transfusions have a negative impact on patient outcome.

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